Schwartzman RJ, Alexander CM et al Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study. Pain 2009;147:107-115.

Design: Randomized clinical trial

Population/sample size/setting:

- 19 patients (18 women, 1 man, mean age 42) who completed a clinical trial of ketamine for CPRS at a university neurology department in Philadelphia
- Eligibility criteria were CRPS diagnosed by IASP criteria for at least 6 months, with lack of success with at least 3 of these therapies: nerve blocks, opioids, NSAIDS, non-opioid analgesics, anticonvulsants, antidepressants, muscle relaxants, and physical therapy
- All patients were taking a stable dose of medication for at least 28 days prior to study entry, and continued these medications at the same dosage for the duration of the study
- Exclusion criteria were pregnancy, substance abuse, glaucoma, thyrotoxicosis, litigation/disability/compensation issues relating to CRPS, and several medical comorbidities such as cardiac, hepatic, renal

Main outcome measures:

- A numerical rating scale (NRS) for pain on a scale of 0-10 was completed for 7 pain variables: current pain in most affected area, pain when brushed lightly, pain with deep pressure, burning pain, joint pain, degree of interference with activity due to pain, and overall pain
- All patients wore an "activity watch" for 2 weeks prior to treatment and for 2 weeks following the study, which recorded the patient's level of activity and, at random intervals, the patient's level of pain
- Additional measurements included thermal pain tolerance, dynamic and static allodynia, pressure pain thresholds, a test of motor function (finger tap rate), and cutaneous temperature
- All patients received four hour intravenous infusions of normal saline with clonidine and midazolam for 10 days (5 days on, 2 days off, 5 days on), and were randomized to placebo (n=10) or ketamine (n=9)
- When the study started, the infusion rate of ketamine was no greater than 25 mg/hour (100 mg ketamine per infusion session); over the course of the 2 year study, the infusion rate was increased to 50 mg/hr (200 mg per session)
- Originally, the study was designed to have 20 patients per treatment arm; however, the study was stopped after 19 patients had completed the study
- The reason for stopping the study was a low placebo response rate, allowing statistical significance to be reached with fewer patients, with ketamine showing an advantage in pain relief
- Pain questionnaires were completed at baseline and again four times following the IV infusions: at 2, 4, 8, and 12 weeks post-treatment
- None of the 7 pain variables changed from baseline in the placebo group, but there were improvements from baseline ($p<.05$) in the ketamine group in 4 of

the 7 variables: pain in the most affected area, burning pain, pain when brushed, and overall pain level

- None of these pain changes was statistically significantly different from baseline throughout all four post-treatment measurements; for example, overall pain was significant at the 2 week measurement but not at any of the subsequent 3 measurements
- Although none of the 7 pain measurements in the ketamine group returned to baseline, all had started to rise from lower levels when the final measurement was done; none of the final pain scores (week 9-12) was significantly different from baseline
- The short form McGill pain questionnaire showed decreases in both the sensory and affective components which lasted for the 12 weeks of follow-up; this did not occur in the placebo group
- The accelerometers in the activity watches did not display significant changes in the level of activity in either treatment group
- Quality of life scores did not change from baseline in either group
- Adverse effects (nausea, headache, tiredness, or dysphoria) were reported by 4 of the 9 ketamine patients and by 2 of the 10 placebo patients; hallucinations and other psychiatric symptoms were not reported in either group

Authors' conclusions:

- Intravenous ketamine at sub-anesthetic doses resulted in a reduction in many pain parameters for CRPS patients
- The small size of the study is a limitation; the results warrant a larger trial with higher doses of ketamine and a longer follow-up period of 5 months

Comments:

- The method of randomization is unclear; concealment of allocation is not described and cannot be assumed; risk of bias may be high
- Multiple endpoints were measured at numerous times, but a primary endpoint is not clearly specified; the analyses may have been data-driven after the data became available (and there is no protocol to compare with)
- When a large number of endpoints are measured without any particular one as the focus of interest, a p value of 0.05 is probably not appropriate, and no adjustment for multiple comparisons was made
- The treatment effect size is small overall; four of seven pain scores showed transient declines, but all four were trending upwards before the end of the study, and three did not significantly change from baseline
- The meaning of the activity watch is not described; presumably, it was worn 24 hours per day, but there is not enough information to determine how it measured pain at random intervals, nor how it measured fewer awakenings at night, nor whether it was worn on the affected limb in the patients who presented with upper extremity symptoms
- The study ended early, with a change in protocol partway through; when this is done with only 19 patients in the study, a small initial change may be mistaken for an important symptom improvement

- The blinding may or may not have been successful; even though few side effects were reported for ketamine, there is no report of whether the patients were able to guess which agent they had received
- The discussion section lists numerous synaptic receptors and ion channels where ketamine may act; while this is of pharmacologic interest, it also may increase the sites at which potential neurotoxicity could occur, and warrants discussion of this possible risk
- Even if the results were valid, no inferences could be made concerning how ketamine would be used in practice: the waning influence of the drug may mean that repeated infusions were required at undetermined intervals
- The infusions were given on an outpatient basis, but there is no description of how long the patients remained in the clinic after the IV infusions were completed, or of which precautions may have been given to the patients when they left the clinic after all had received midazolam and/or ketamine

Assessment: Inadequate for any inferences about the effectiveness of IV ketamine for CRPS (risk of bias, small sample size, small effect size, unclear primary outcome)